Remarks/Arguments

The specification has been amended to add subject matter from literature references that were incorporated by reference in their entirety by the incorporation by reference statement in paragraph [0083] of the specification as filed. Support for the amendment in paragraph [0067] is in Kotake et al., J. Clin. Invest. 103(9):1345-1352, at page 1349, second column, lines 17-19. Support for the amendment of paragraph [0070] is in Wong et al., Lupus 9:589-593 (2000), at page 590, second column, lines 20-23. Support for the amendment of paragraph [0072] is in Matusevicius et al., Mult. Scler. 5(2):101-4 (1999), Abstract. Copies of these references are enclosed with the attached Second Supplemental Information Disclosure Statement. As attested by the enclosed Declaration on Incorporation by Reference, the amendatory material consists of the same material as in the referenced papers, which are incorporated by reference in their entirety in the above-indicated application. Thus, the amendments to the specification do not introduce new matter.

Claims 14-16 and 18-28 are pending in this application and stand rejected on various grounds. Claim 14 has been amended. Support for the amendments is throughout the specification and in amended paragraphs [0067], [0070], and [0072]. Specific support for the phrase "compared to a healthy individual" is in paragraph [0072], as currently amended.

Claim Objections

Claim 14 has been objected to "because the clam can be interpreted as reading on a mammalian subject that has exhibited increased levels of IL-17, or alternatively, a mammalian subject motivated to express an elevated level of IL-17." The current amendment of claim 14, which follows the Examiner's suggestion, is believed to overcome this objection.

Claim Rejections – 35 USC § 112, first paragraph – enablement

Claims 14-16 and 18-28 remained rejected under 35 USC § 112, first paragraph, "regarding lack of enablement for methods of treating all possible diseases characterized by increased IL-17." In addressing Applicants' arguments submitted in addressing a previous similar rejection, the Examiner notes: (1) the data presented in the specification were obtained by in vitro experiments and it *"is known in the art that in vitro experiments do not always*

extrapolate to in vivo results;" (2) although the data presented in the specification *"establish a biological role for IL-23 in promoting IL-17 production in vitro, there is no in vivo evidence showing that administration of an anti-IL-23 or anti-IL-23 receptor antibody would be effective in treating any disease in an intact animal;"* (3) *"Marshall (Science, 2006, Vol. 311, p. 1688-1689) teaches that in vivo administration of antibodies may have unpredictable consequences,"*, describing a clinical study *"in which patients given experimental antibodies developed severe, life-threatening reactions to the antibodies."* From this the Examiner concludes that *"one of ordinary skill in the art could predict that the claimed method could effectively treat each of the recited diseases without further, undue in vivo experimentation."* (Office Action, page 4).

Applicants disagree and respectfully traverse the rejection.

Initially, it is emphasized that the proper legal standard for enablement determination is not whether *in vitro* experiments in general "always" extrapolate to *in vivo* results, rather whether a person of ordinary skill in the pertinent art would reasonably conclude that the *in vivo* data presented by Applicants are more likely than not to correlate with the claimed *in vivo* application(s).

Marshall et al. is completely irrelevant for this determination. First of all, Marshall et al. report complications in a clinical trial conducted with an agonist anti-CD28 monoclonal antibody TGN1412 aimed at treating leukemia and autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis. Since the TGN1412 antibody targeted an antigen (CD28) different from and unrelated to both IL-23 and the IL-23 receptor and was an agonist antibody, the catastrophic side effects observed during the human clinical trials conducted with the anti-CD28 antibody have no bearing on the question whether antibodies in general, or antagonist anti-IL-23 or anti-IL-23 receptor antibodies in particular, would be reasonably expected to have such side effects. Indeed, since as of today at least 17 therapeutic monoclonal antibodies obtained FDA approval, it would be unreasonable to assume that antibodies in general, not to mention anti-IL-23 or anti-IL-23 receptor antibodies in particular, are likely to invoke serious side effects when administered to humans. This is supported by the Marshall et al. article itself, which, on page 1689 cites David Hafner of Harvard Medical School, Boston, to say: "I wouldn't have thought [an accident like this] could happen." The fact that the observed side-effects were specific for the CD28 antigen is further supported by Johannes Lower's statements suggesting that further research is needed

"to define better animal models of the human response to CD28 agonists," and "extra precaution should be taken "when antibodies are used to stimulate rather than neutralize components of the immune system." Finally, it is noted that assessment of potential side effects of a drug candidate is properly within the purview of the FDA and not the Patent Office, and completion of human clinical trials (which would be the only guarantee that unwanted side effects do not occur) is not a condition for patentability.

In further support of the efficacy and safety of the treatment of inflammatory diseases characterized by elevated expression of interleukin 17 (IL-17) using anti-IL-23 antibodies, as taught in the present application, enclosed is a copy of Bowman et al., Current Opinion in Infectious Diseases, 19:247-252 (2006) – copy enclosed. While the authors consider the potential side effects of antibody therapy targeting the IL-23/L-17A axis, they conclude "specific blockade of IL-23 or factors downstream of IL-23 (i.e. IL-17A and IL-17F) may be an effective and safer therapy for immune-mediated inflammatory diseases than broad-spectrum immune modulators such as p40 antagonists." (Page 250, last sentence). The authors specifically note: "It is likely that targeting interleukin-23 or interleukin-17A alone, as opposed to targeting interleukin-12 or interleukin-23 together, will reduce the patients' risk of developing treatment-related infections." These observations are confirmed by Zhang et al., International Immunopharmacology 7:409-416 (2007) – copy enclosed, who suggest that specifically targeting IL-23 and IL-17 one can avoid the side-effects of anti-IL-2 targeted antibody therapy, which appears to increase the risk of Salmonellae and Mycobacteria infections. (Page 414, first column). Therefore, "[c]ontrolling thee xpression/production of IL-23 and IL-17 is an approach that would allow the development of a novel treatment strategy with more anti-inflammatory efficacy and potentially lesser effects on host defenses." (Abstract)

In view of these arguments and the submitted evidence, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 USC § 112, first paragraph – written description

Claims 14-16 and 18-28 were rejected under 35 U.S.C. § 112, first paragraph as allegedly containing new matter in their recitation of a method comprising administering anti-IL-23 antibodies or anti-IL-23 receptor antibodies to a mammalian subject "determined to express an

elevated level of IL-17." According to the rejection, this claim limitation "is not expressly asserted, nor does it flow naturally from the Specification as originally filed."

The rejection is respectfully traversed.

The specification, as originally filed, discloses methods and pharmaceutical compositions for the treatment of inflammatory diseases characterized by elevated expression of IL-17. Such diseases, along with literature references discussing determination of IL-17 levels, are disclosed on pages 22 and 23 of the specification. Parts of the cited references discussing determination of the IL-17 levels have now been added to the specification. Since the claimed treatment methods are directed to the treatment of an inflammatory disease characterized by elevated expression of IL-17, it follows that determination that the IL-17 level is elevated needs to precede administration of an anti-IL-23 or anti-IL-23 antibody. Therefore, Applicants submit that the newly added limitation does naturally follow from the specification as originally filed and does not introduce new matter. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge all fees required or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39766-0125A**.

Respectfully submitted,

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